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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/693,754 | 10/20/2000 | Neil Berinstein | 13115 | 7885 |

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| EXAMINER | |
|---|---|
| WEHBE, ANNE MARIE SABRINA | |
| ART UNIT | PAPER NUMBER |
| 1633 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 02/12/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/693,754 | BERINSTEIN ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2 and 4-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/06 has been entered. No claim amendments have been filed with this RCE. Applicant's remarks, however, also submitted on 11/17/06 have been entered. Claims 1-2, and 4-27 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in the previous office action.

### *Claim Rejections - 35 USC 103*

The rejection of claims 1-2, 4-17, and 20 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US Patent No. 6,127,116 (10/3/00), filed on 3/4/97 and hereafter referred to as Rice et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, is maintained. Applicant's arguments have been fully considered but have not been

found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that Hurpin et al. does not show the administration of two different forms of antigens, does not teach administration directly into a lymph node, and further teaches away from administering the antigen to different sites. The applicant further teaches that Hodge, while teaching a prime-boost strategy, does not teach intranodal administration. The applicant then states that neither reference alone or in combination is a proper 103 reference.

In response, it is first noted that the rejection of record is based on the combined teachings of Hurpin et al. Hodge et al., Rice et al. and Lehner et al., and not on any one of those references alone. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, Hurpin et al. was cited for teaching teaches the generation of anti-53 CTL responses in mice following intrasplenic injection of ALVAC encoding p53 (Hurpin et al., page 209, column 2, second paragraph, and page 210, column 2, last paragraph, and page 211, Figure 1, panel b). While Hurpin et al. does not specifically teach a boosting step in addition to a priming step, Hurpin et al. does teach that the route of administration is also important for boosting the response (Hurpin et al., page 211, column 1, paragraph 1). Further, please note that intrasplenic injection is administration to a lymphatic tissue. Thus, Hurpin et al. provides clear teachings and motivation to administer antigen to a lymphatic site.

In addition, Hurpin does not teach away from using a prime-boost strategy, Hurpin on page 221 shows that the route of administration is important for not just a priming step, but also

for subsequent "boost" administrations. Hurpin shows that 3 administrations of ALVAC encoding p53 using the intrasplenic route is effective in generating CTL. Hurpin also shows that 3 intravenous administrations is effective, but that 3 subcutaneous administration was not. Hurpin then tested whether the priming route of administration, i.e. the first administration, is more important in generating immune responses than the boosting route of administration by using a prime of 1 intravenous with two subcutaneous boosts and showed that even with an intravenous priming step, the subcutaneous route, which was already demonstrated to be ineffective in CTL generation, was not effective in CTL generation. This shows that route of administration is important in not just the priming, but in the boosting step as well. There is nothing in Hurpin that teaches away from multiple antigen administrations, i.e. prime and boost, and nothing to teach away from using lymphatic administration.

The rejection of record further recognized that Hurpin by itself does not teach direct injection to a lymph node or the use of a prime-boost strategy where the antigen is in different forms. Hodge et al. was cited to supplement Hurpin et al. by teaching a diversified prime and boost protocol for enhancing T-cell immunity and antitumor immune responses. Specifically, Hodge et al. teaches that priming an anti-tumor immune response by administering a vaccinia virus encoding CEA followed by boosting with an avipox virus (ALVAC) encoding CEA results in the generation of anti-CEA immune responses superior to those generated by the use of either vector alone (Hodge et al., page 759, and page 766, Table 3). Please note that Vaccinia virus encoding CEA and ALVAC encoding CEA represent different forms of the same tumor antigen since vaccinia is a cowpox virus and ALVAC is an avipox virus. Applicant's argument that Hodge does not teach intranodal administration is not compelling since Hodge was not cited for

this teaching. Hodge was cited for teaching the diversified prime-boost strategy. Hurpin already provided sufficient motivation for lymphatic administration and Rice and Lehner et al. was further cited to provide specific motivation for direct intranodal administration.

The applicant argues that neither Rice et al. nor Lehner et al. supplement Hurpin or Hodge by providing the requisite suggestion and reasonable expectation of success for generating immune responses according to the instant methods claimed by using direct administration "into a lymph node". The applicant argues that Rice only provides a laundry list of possible routes of administration, one of which includes administration to lymph nodes, and that this is not sufficient to motivate the artisan to use lymph node administration. In response, it is clear from the indicated passage from Rice reproduced in the applicant's response that Rice does more than just include lymph node administration in a "laundry list" of administration routes. Rice in fact teaches that administration directly or indirectly to lymph nodes is a preferred method of immunization. Thus, of the genus of parenteral routes taught by Rice, Rice specifically points to the use of lymph node administration. Therefore it is maintained that Rice does in fact provide specific motivation for lymph node immunization.

Regarding the required "reasonable expectation of success", the applicant argues that at best Rice only provides an invitation to try lymph node administration and Lehner does not supplement Rice because the Lehner method teaches "in the proximity of" the iliac lymph nodes and does not teach administration "to" the iliac lymph node. In response, Rice already provides the motivation to generate immune responses by administrating directly to a lymph node. Lehner provides a reasonable expectation that delivery of antigen to lymph nodes would prime an immune response by demonstrating the delivery of the antigen such that the lymph node is

targeted generates increased immune responses to the antigen as compared to other routes of administration. As stated in the previous office action, Lehner et al. showed that a direct comparison of intramuscular versus intradermal versus targeted iliac lymph node immunization revealed that targeted iliac lymph node administration of antigen resulted in increased T and B cell mediated antigen-specific immune responses (Lehner et al., page S489, and page S491). The applicant argues that Lehner used targeted iliac lymph node administration in 1994, 5 years earlier than the reference of record, Lehner et al. (1999) and that this shows that Lehner was not motivated to use direct lymph node administration and continued to use targeted iliac lymph node administration. However, the earlier paper by Lehner et al. is irrelevant to the rejection of record. Lehner et al. (1999) was cited for providing motivation to deliver antigen to a lymph node, not for "direct" lymph node administration. The specific teachings for direct lymph node administration was provided by Rice et al. Further, the instant rejection is not based solely on the teachings of Lehner, but on the combination of teachings of Hurpin, Hodge, Rice, and Lehner. Thus, by demonstrating that targeting antigen to the iliac lymph node results in increased T and B cell mediated antigen-specific immune responses over other routes of administration, Lehner et al. provides motivation for substituting the direct lymph node administration taught by Rice et al. over the intrasplenic or intramuscular administration routes taught by Hurpin et al. and Hodge et al.

Thus, for reasons of record, the rejection stands.

The rejection of claims 18-19 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15,

No. 6/7, 759-768, US Patent No. 6,127,116 (10/3/00), filed on 3/4/97 and hereafter referred to as Rice et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20, and further in view of Zaremba et al. (1997) Canc. Res., Vol. 57, 4570-4577 and Salgaller et al. (1996) Canc. Res., Vol. 56, 4749-4757, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Applicant's arguments are based on their previous argument that Hurpin in view of Hodge, Rice, and Lehner do not provide the requisite motivation and reasonable expectation of success to arrive at the instant invention as claimed. These arguments have been fully considered and addressed in detail above and have not been found persuasive. Applicant's further argument that Zaremba et al. and Salgaller et al. do not overcome the deficiencies of Hurpin, Hodge, Rice, and Lehner is not persuasive as the teachings of Hurpin, Hodge, Rice, and Lehner stand, as discussed above, and Zaremba and Salgaller were not cited to teach lymph node administration, rather these references were cited to provide teachings and motivation to immunize with tumor antigens which comprise the sequence YLSGADLNL or YLEPGPVTV. The applicant has not traversed these teachings, therefore, the rejection of record stands.

The rejection of claims 21-27 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US Patent No. 6,127,116 (10/3/00), filed on 3/4/97 and hereafter referred to as Rice et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20 above, and further in view of Barnett et al. (1997) Vaccine, Vol. 15(8),

869-873, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Applicant's arguments are based on their previous argument that Hurpin in view of Hodge, Rice, and Lehner do not provide the requisite motivation and reasonable expectation of success to arrive at the instant invention as claimed. These arguments have been fully considered and addressed in detail above and have not been found persuasive. Applicant's further argument that Barnett does not overcome the deficiencies of Hurpin, Hodge, Rice, and Lehner is not persuasive as the teachings of Hurpin, Hodge, Rice, and Lehner stand and Barnett was not cited to teach lymph node administration, rather Barnett was cited to provide teachings and motivation to immunize using a prime/boost vaccination strategy which includes a priming step with a nucleic acid encoding an antigen and a boosting step with a protein form of the antigen. The applicant has not traversed these teachings, therefore, the rejection of record stands.

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the

USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER